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[54] GROWTH ARREST HOMEBOX GENE

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[51] Int. Cl.⁶ C12N 15/12; C12N 15/63;
C12N 1/21; C12N 5/10[52] U.S. Cl. 435/69.1; 435/243; 435/320.1;
435/325; 536/23.5[58] Field of Search 536/23.5; 435/69.1,
435/69.4, 320.1, 252.3; 530/399

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Nabel et al *Science* 249:1285-1288 (1990).Donald B. Smith, et al., Single-Step Purification of Polypeptides Expressed in *Escherichia coli* as Fusions with Glutathione S-transferase, *Gene* 67: 31-40 (1988).Moshe Y. Flugelman, MD, et al., Low Level in Vivo Gene Transfer into the Arterial Wall Through a Perforated Balloon Catheter, *Circulation* 85: 1110-1287 (1992)."The Growth Arrest-Specific Gene, gas1, is Involved in Growth Suppression," Del Sal et al., *International Centre for Genetic Engineering and Biotechnology* Aug. 21, 1992, pp. 595-607."Cloning of Senescent Cell-Derived Inhibitors of DNA Synthesis Using an Expression Screen", Noda et al. *Experimental Cell Research*, 211, 1994 pp. 90-98."CHOP" (GADD153) and its Oncogenic Variant, TLS-CHOP, Having Opposing Effects on the Induction of G₁/S Arrest, Barone et al. *Genes & Development*, 8, 1994, pp. 453-464."Mox-1 and Mox-2 Define a Novel Homeobox Gene Subfamily and are Differentially Expressed during Early Mesodermal Patterning in Mouse Embryos", Candia et al., *Development*, 116, Aug. 28, 1992, pp. 1123-1136."Arterial Gene Transfer Using Pure DNA Applied Directly to a Hydrogel-Coated Angioplasty Balloon," Riessen et al., *Human Gene Therapy*, 4, 1993, pp. 749-758.Antisense c-myc Oligonucleotides Inhibit Intimal Arterial Smooth Muscle Cell Accumulation in Vivo, Simons et al. *Nature*, vol. 359, Sep. 3, 1993, pp. 67-70."Site-Specific Gene Expression In Vivo by Direct Gene Transfer Into the Arterial Wall", Nabel et al. *Reports*, Apr. 11, 1990, pp. 1285-1288.

Exhibit A is the gene sequence for the rat Gax cDNA (2244 base pairs) submitted by Kenneth Walsh, released to the public Feb. 28, 1993.

Exhibit B₁ is a gene sequence for Mox-1 (2182 base pairs) (mistakenly designated "Mox-2") submitted by A.F. Candia to New GenBank and created on Sep. 25, 1992.Exhibit B₂ is the same gene sequence as Exhibit B₁ except the former designation "Mox-2" has been corrected to read Mox-1.

Exhibit C is the partial gene sequence for mouse Mox-2A submitted by Candia A by A.F. Candia to GenBank and created on Oct. 5, 1992.

Exhibit D is the revision of Exhibit C to show the 1440 base pair mouse Mox-2 sequence on Mar. 6, 1993.

Candia et al., *Nucleic Acids Research* (1993) 21(21):4982."Molecular Cloning of a Homeobox Transcription Factor From Adult Aortic Smooth Muscle", Patel et al., *The Journal of Biological Chemistry*, vol. 267, No. 36, Dec. 25, 1992, pp. 26085-26090."Molecular Cloning of a Diverged Homeobox Gene that is Rapidly Down-Regulated During the G₀/G₁ Transition in Vascular Smooth Muscle Cells", Gorski et al., *Molecular And Cellular Biology*, vol. 13, No. 6, Jun. 1993, pp. 3722-3733."Homeobox Transcription Factor Regulation in the Cardiovascular System", Gorski et al., *TCM*, vol. 3, No. 5, 1993, pp. 184-190."Cloning and Sequence Analysis of Homeobox Transcription Factor CDNAs With an Inosine-Containing Probe", Gorski et al. *Short Technical Reports*, vol. 16, No. 5, 1994.

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[57] ABSTRACT

A novel growth arrest homeobox gene has been discovered and the nucleotide sequences have been determined in both the rat and the human. The expression of the novel homeobox gene inhibits vascular smooth muscle cell growth. The growth arrest homeobox gene hereinafter referred to as the "Gax gene" and its corresponding proteins are useful in the study of vascular smooth muscle cell proliferation and in the treatment of blood vessel diseases that result from excessive smooth muscle cell proliferation, particularly after balloon angioplasty.

27 Claims, 10 Drawing Sheets

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